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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/625,049	07/24/2000	Reinhilde Schoonjans	DECLE18.001C1	6634

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 03/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/625,049	Applicant(s) SCHOONJANS ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-66* is/are pending in the application.

4a) Of the above claim(s) *51-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *02 January 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 43-50 and 61-66 in Paper No. 10 is acknowledged.

2. Claims 51-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in Paper No. 10.

3. Claims 43-50 and 61-66 are under examination.

Drawings

4. The examiner acknowledges the proposed drawing corrections of drawings of pages 3, 4, 6, 8-10, 12, 13, and 14 filed 1/2/02. Applicant is required to summit corrected drawings in response to this Office Action.

Specification

5. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 28, line 12, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

b. The first line of the specification should be updated to recite "This is a continuation of International Application PCT/EP99/00477, with an international filing

date of January 23, 1998, published in English under PCT Article 21(2) and now abandoned" (see MPEP 1895.01(F)).

Appropriate correction is required.

Priority

6. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Europe on 1/23/98. It is noted, however, that applicant has not filed a certified copy of the EP 98200193.5 application as required by 35 U.S.C. 119(b). Therefore, the claims in the instant application are granted the priority date of PCT/EP99/00477 which is 1/25/99.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 43-44, 46-49, 61-62, 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter (U.S. Patent 5,648,237, issued 7/15/97) and further in view of Chester et al (TIBTECH 13:296, 1995).

The claims recite a multipurpose heterodimeric antibody comprising CL and VL domains interacting with CH1 and VH domains wherein the CH1 domain is not linked to a hinge region and further the antibody comprises two or more other molecules coupled to the CH1-VH and CL-VL wherein the coupling takes place with a linker of at least one amino acid, wherein the molecule is coupled to the C-terminal of the CH1 and CL domains, , wherein the antibody is multivalent, bispecific, multispecific, and compositions comprising such. For this rejection the intended use as a pharmaceutical preparation in claim 65 and as a diagnostic preparation in claim 66 are given no

patentable weight. In addition, for this rejection the phrase "one further purpose" is being interpreted to mean a linker (an SH) and multispecific and multivalent is interpreted to mean bispecific and bivalent.

Carter teach antibody Fab-SH and bispecific antibodies comprising Fab antigen binding fragments and the SH is from a single thiol cysteinyl residue that is used in place of the hinge region and can be placed at the C-terminal of the light chain or the heavy chain (see column 4-5, column 8, lines 20-23, column 13, lines 10-12). Carter also teach immunotoxins (column 17, lines 18 to column 18, line 22) that can be coupled to the Fab. Carter et al does not specifically teach another molecule coupled to the C-terminal of both constant domains. This deficiency is made up for in the teachings of Chester et al.

Chester et al teach a Fab fusion protein comprising a toxin or enzyme at the C-terminal of the CL domain.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the Fab-SH antigen binding fragment of Carter and couple a toxin or enzyme to the CL domain as taught by Chester et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the Fab antigen binding fragment of Carter and couple a toxin or enzyme to the CL domain as taught by Chester et al because Carter teach the Fab antigen binding fragment can be coupled to toxins or other molecules and the coupling can be through the C-terminal of the light chain constant domain or the

heavy chain constant domain (see column 4-5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the Fab antigen binding fragment of Carter and couple a toxin or enzyme to the CL domain as taught by Chester et al because Chester et al teach a Fab fragment fusion protein coupled to another molecule at its C-terminal of the CL domain and the avidity can be improved by making the univalent interactions bivalent (see right column). Thus, it would have been obvious to one of ordinary skill in the art to produce a bivalent Fab as taught by Carter and couple to the C-terminal of the CL domain another molecule as taught by Chester et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 43-50 and 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter (U.S. Patent 5,648,237, filed 5/3/95) and further in view of Muller et al (FEBS Letters 422:259-64, 1998) and Tutt et al (The Journal of Immunology 147:60-69, 1991). For this rejection the intended use as a pharmaceutical preparation in claim 65 and as a diagnostic preparation in claim 66 are given no patentable weight. In addition, for this rejection multispecific and multivalent is interpreted to mean bispecific and bivalent.

Claims 43-44, 46-49, 61-62, 64-66 have been described supra. Claims 45, 50, and 63 recite wherein an sFv is coupled to each CH1 and CL domains and the antibody is a trispecific antibody.

Carter has been described supra. Carter does not teach a trispecific antibody comprising a sFv coupled to each CH1 and CL domain. This deficiency is made up for in the teachings of Muller et al and Tutt et al.

Muller et al teach a ScFv coupled to each of a CH1 and CL domain. Muller et al also teach activation of CTL and NK by CD2 is useful and requires a second CD2 antibody (see page 259, right column).

Tutt et al teach trispecific antibodies comprising Fab fragments which are used to signal the TCR/CD3 complex and CD2 to activate cytotoxic T cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the Fab antigen binding fragment of Carter and couple a scFv to each of the CH1 and CL domains as taught by Muller et al and also produce a trispecific antibody as taught by Tutt et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the Fab antigen binding fragment of Carter and couple a scFv to each of the CH1 and CL domains as taught by Muller et al and also produce a trispecific antibody as taught by Tutt et al because Carter teach the Fab antigen binding fragment can be coupled to toxins or other molecules and the coupling can be through the C-terminal of the light chain constant domain or the heavy chain constant domain (see column 4-5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the Fab antigen binding fragment of Carter and couple a scFv to each of the CH1 and CL domains as taught by Muller et al and also produce a trispecific antibody as

taught by Tutt et al because Muller et al teach that the CH1-CL disulfide bridge was assembled (see abstract) and the scFv molecules bind antigen and "the advantage of this format is a longer reach to far apart antigens compared to smaller bispecific variants, which is expected to be advantageous for bridging tumor cells with effector cells" (see page 259, right column) and "it was shown that such complex molecules comprising heterodimers of three different Ig domains, each with disulfide linkages between them, can be functionally formed in E. coli (see page 263, left column). Moreover, it would have been obvious to one skill in the art to produce a trispecific antibody because Tutt et al teach trispecific antibodies have advantages in the destruction of unwanted cells by unprimed effectors (see abstract) and Tutt et al has produced a trispesific antibody which as a single molecule can activate T cells with two Fab' arms and retarget them with a third arm (see page 61, right column top). Thus, it would have been obvious to produce a Fab comprising two scFv coupled to the C-terminal of both CH1 and CL in order to produce a trispecific molecule with the advantages taught in Tutt et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879